Synthetic Strategies of Marine Polycyclic Ethers via Intramolecular Allylations: Linear and Convergent Approaches

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ABSTRACT

Strategies for the synthesis of polycyclic ethers based on intramolecular allylations are overviewed. The intramolecular condensation of allylic stannanes and aldehydes is a powerful tool for the synthesis of oxepane derivatives. The reaction is successfully applied to the iterative total synthesis of hemibrevetoxin B (**2**). Further, the intramolecular allylation of α-acetoxy ethers provides an efficient method for the convergent synthesis of polycyclic ethers. The usefulness of the latter strategy is demonstrated in the convergent total synthesis of gambierol (**4**).

Introduction

Since the discovery of brevetoxin B (**1**) in 1981,[1] a number of polycyclic ethers such as hemibrevetoxin B (**2**),[2] ciguatoxin (**3**),[3] gambierol (**4**),[4] and yessotoxin (**5**)[5] have been isolated from marine organisms (Scheme 1). These compounds show potent neurotoxicity by binding to the ion channels and cause massive fish kills and human food poisoning.[6] Since further studies are hampered by the limited availability from nature, chemical synthesis has been the sole realistic way to obtain sufficient amounts of the polycyclic ethers. Moreover, the unusual structures of these compounds are particularly attractive targets for synthetic chemists. Thus, a variety of strategies for the construction of trans-fused polycyclic ether skeletons have been developed and applied to the total syntheses of these natural products.[7−13] In this Account, we report our linear and convergent approaches to the synthesis of polycyclic ethers based on an "intramolecular allylation" methodology.

Background

In the late 1980s, one of the present authors studied acyclic stereocontrol via allylic organometallic compounds;[14] the reaction of aldehydes **6** with crotylstannane **7** in the presence of $BF_3{\cdot}OEt_2$ gave predominantly the syn-homoallylic alcohols **8** regardless of the stereochemistry of the crotyl unit (Scheme 2). Similarly, the γ-alkoxy-substituted allylic stannanes **9** produced the syn-homoallylic diol derivatives **10** upon treatment with aldehydes.[15]

The intramolecular reaction of the γ-alkoxy-substituted allylic stannanes **11** bearing an acetal at the end of the carbon chain gave stereoselectively the corresponding β-alkoxy cyclic ethers **12** in good to high yields (Scheme 3).[16] The trans-stereochemistry at the α and β positions matched well that of the ether framework of polycyclic ethers. The stereoselectivity of the reaction of **11** can be explained by a well-accepted acyclic transition state model (Figure 1).[14] To avoid the 1,3-diaxial repulsion, the allylic stannane and the oxocabenium ion moieties are oriented to pseudo-equatorial positions leading to the trans-cyclic ether **12**.

Iterative Synthesis of Polycyclic Ethers via the Intramolecular Allylation of Aldehydes

Encouraged by the above finding, we investigated the iterative synthesis of polycyclic ethers as shown in Scheme 4.[17] Treatment of the allylic ether **13** with *sec*-BuLi/tetramethylethylenediamine (TMEDA) followed by trapping of the resulting allylic anion with *n*-Bu_3SnCl gave the allylic stannane **14** (76%), which was oxidized to produce the cyclization precursor **15**. The allylic stannane **15** was then subjected to cyclization with $BF_3{\cdot}OEt_2$ to give the 6,7-bicyclic ether **16** in quantitative yield with high stereoselectivity. Manipulation of the hydroxy and vinyl groups of the product and iteration produced the 6,7,7,6-tetracycle **17**, which is a part of the cyclic ether skeleton of brevetoxin B. This reaction was recognized as one of the most powerful methods for the synthesis of oxepane derivatives[18] and has been employed for synthetic studies of polyclic ethers.[19]

Isao Kadota was born in 1965 in Kochi, Japan. After receiving his B.S. and M.Sc. degrees from the Department of Chemistry, Kochi University, under the guidance of Professor Hiyoshizo Kotsuki, he joined Tohoku University and obtained his Ph.D. degree in 1993 under the direction of Professor Yoshinori Yamamoto. He has been granted a Fellowship of the Japan Society for the Promotion of Sciences (JSPS) for Young Scientists (1992−1993). He was appointed as an assistant professor at Tohoku University in 1993 and promoted to an associate professor in 1996. He joined the group of Professor Scott D. Rychnovsky at the University of California, Irvine, as a visiting researcher (1999−2000). He was awarded the Japan Chemical Society Award for Young Chemist (1997). His current research interests are focused on the development of new synthetic reactions and their application to the total synthesis of natural products.

Yoshinori Yamamoto was born in 1942 in Kobe, Japan. He received his M.Sc. and Ph.D. degrees from Osaka University and was appointed as an Instructor at Osaka University in 1970. While he was working as an Instructor at Osaka University, he went to Professor H. C. Brown's research group at Purdue University as a Postdoctoral Associate (1970−1972). In 1977, he was appointed as an Associate Professor at Kyoto University. In 1986, he moved to Tohoku University to take up his present position, Professor of Chemistry. He was also holding a Professorship at the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University (1996−2004). He was awarded the Chemical Society of Japan for Young Chemists (1976), the Chemical Society of Japan Award (1996), and Humboldt Research Award (2002). He is the Regional Editor of *Tetrahedron Letters* and Volume Editor of *Science of Synthesis*, and he was the President of the International Society of Heterocyclic Chemistry (2000−2001). He is the project leader of the 21 Century COE Program of MEXT "Giant Molecules and Complex Systems, Chemistry Group of Tohoku University" (2002−2006). He has a wide range of research interests in synthetic organic and organometallic chemistry. His recent work focused on the use of transition metal complexes and Lewis acids as catalytic reagents in organic synthesis and synthesis of complex natural products.

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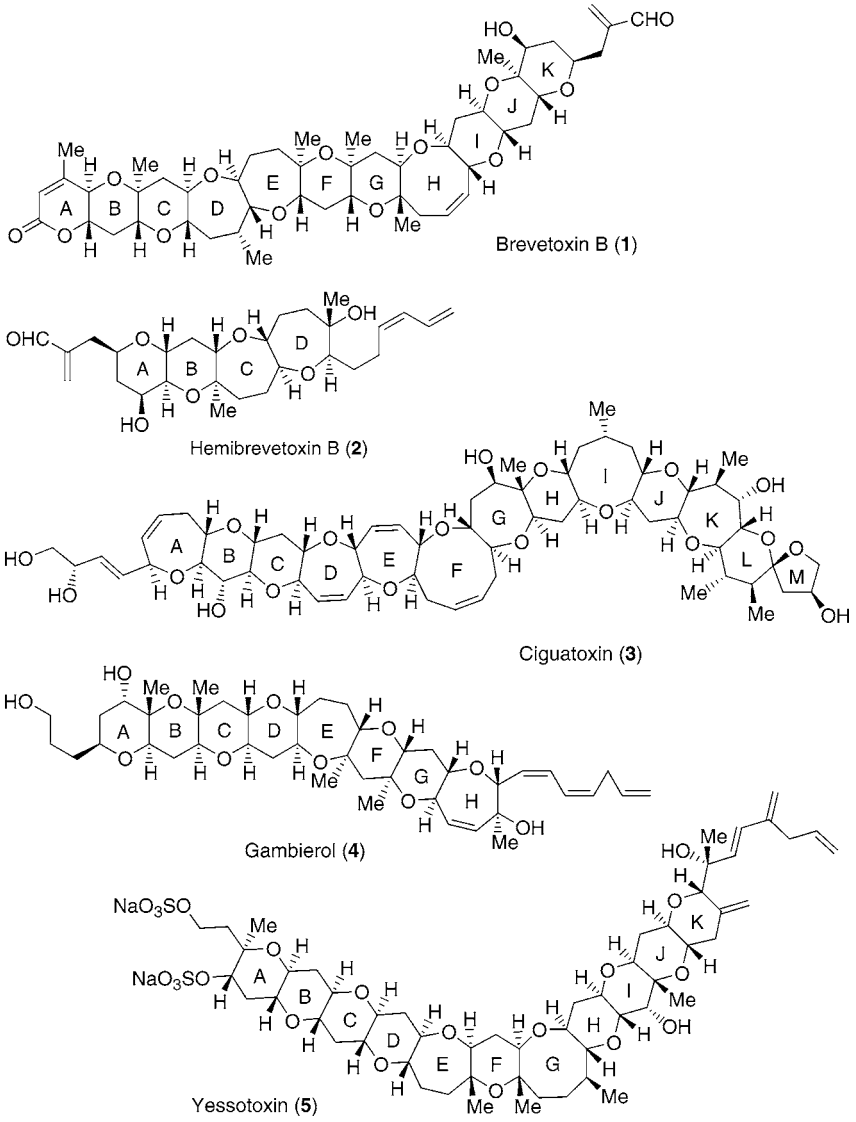
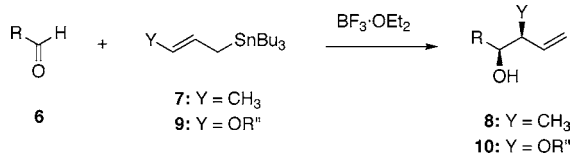
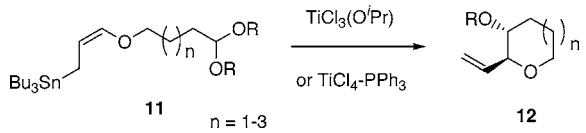
Scheme 1. Examples of Marine Polycyclic Ethers



Scheme 2



Scheme 3



To demonstrate the usefulness of this methodology, we next examined the total synthesis of hemibrevetoxin B (**2**) as shown in Scheme 5.[10c,e] Cyclization of **18** with $BF_3{\cdot}OEt_2$ proceeded smoothly to afford the tricyclic compound **19** as the sole product in 94% yield. Further transformation provided the allylic ether **20**, which was subjected to the usual allylstannane synthesis. However, we encountered a serious problem at this stage. The reaction of **20** gave the desired allylstannane **21** in only 16% yield.[10c] Deprotonation of the sterically bulky allylic ether **20** was very slow, and decomposition of the resulting allylic anion became competitive when a prolonged reaction time was employed.

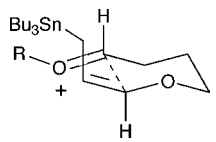
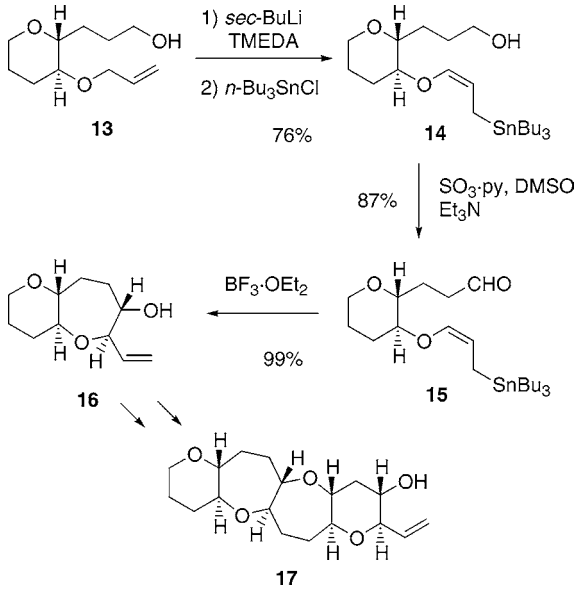


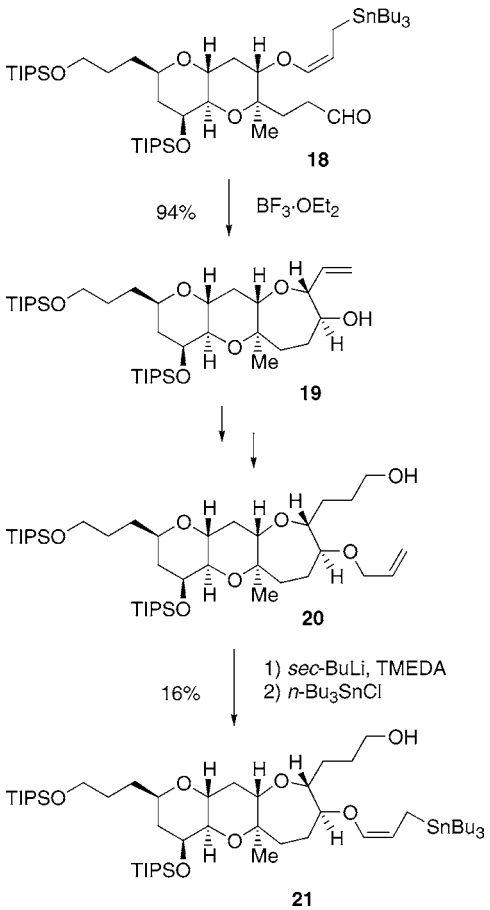
FIGURE 1. Acyclic transition state model.

After several unfruitful attempts, we developed a new synthetic route to γ-alkoxyallylstannanes using an acetal cleavage as shown in Scheme 6.[20] Reaction of the alcohol **22** with γ-methoxyallylstannane **23** in the presence of a catalytic amount of camphorsulfonic acid (CSA) proceeded smoothly to give the mixed acetal **24** as a 1:1 mixture of diastereomers in 93% yield. Treatment of **24** with iodotrimethylsilane (TMSI)/hexamethyldisilazane (HMDS) afforded the enol ether **25** in 85% yield.[21] It is notable that both the acetal formation and cleavage

Scheme 4



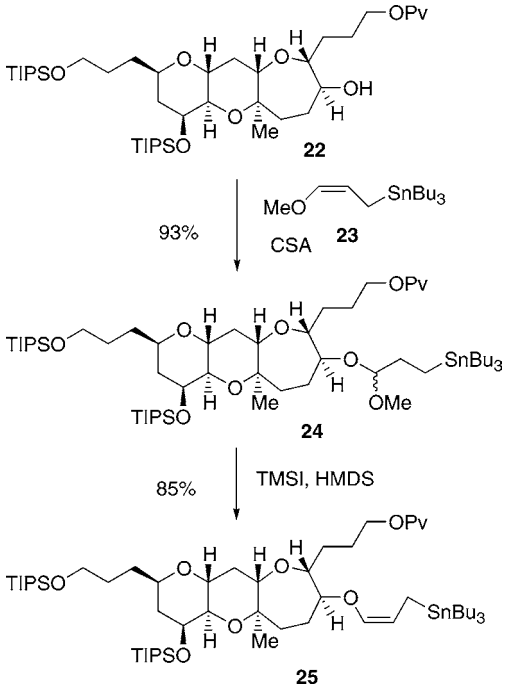
Scheme 5



proceeded under mild reaction conditions and were not affected by the bulkiness of the substrate.

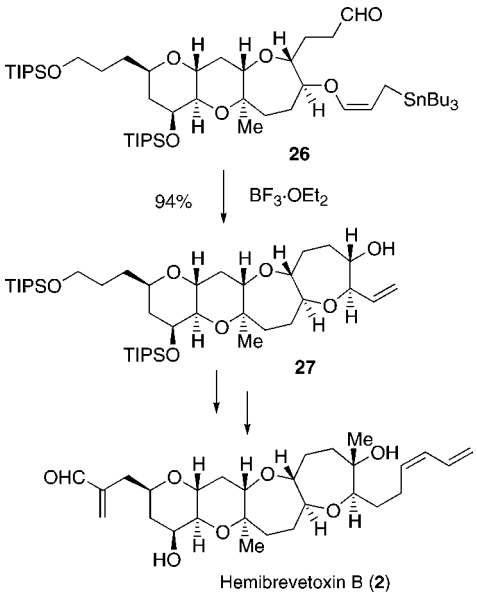
The final sequence of the synthesis is shown in Scheme 7. Treatment of **26**, prepared from **25** via deprotection and oxidation, with $BF_3{\cdot}OEt_2$ provided the tetracyclic ether **27** as the sole product in 94% yield. Further modification of the side chains completed the total synthesis of hemibrevetoxin B (**2**). The total number of the steps

Scheme 6[a]



[a] CSA = camphorsulfonic acid; TMSI = iodotrimethylsilane; HMDS = hexamethyldisilazane.

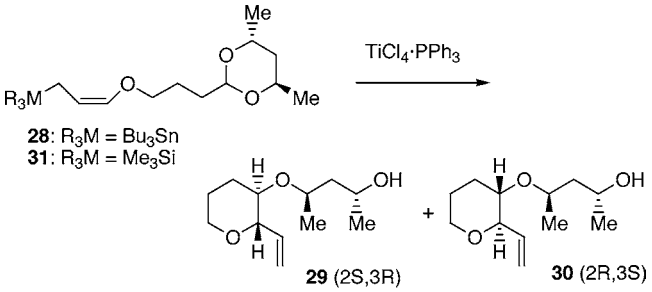
Scheme 7



is 56, and the overall yield is 0.75%.[10e] Although the iterative strategy employed makes the synthesis considerably longer, the target molecule **2** was obtained in high yield.

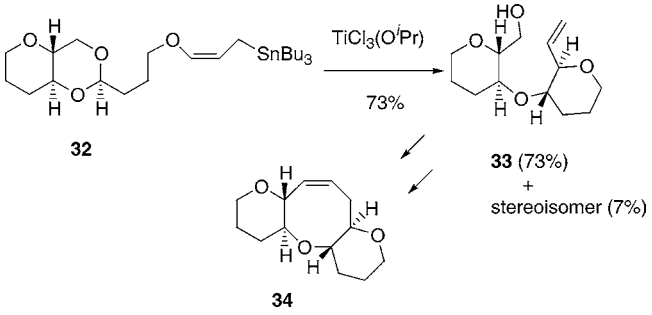
The power of the intramolecular allylation of aldehydes as a tool for the synthesis of medium-sized cyclic ethers was demonstrated in this study. Furthermore, the new method for the synthesis of γ-alkoxyallylstannanes via an acetal cleavage allowed us to design substrates having a variety of functional groups. This finding was quite important for our next subject, the convergent synthesis of polycyclic ethers.

Scheme 8

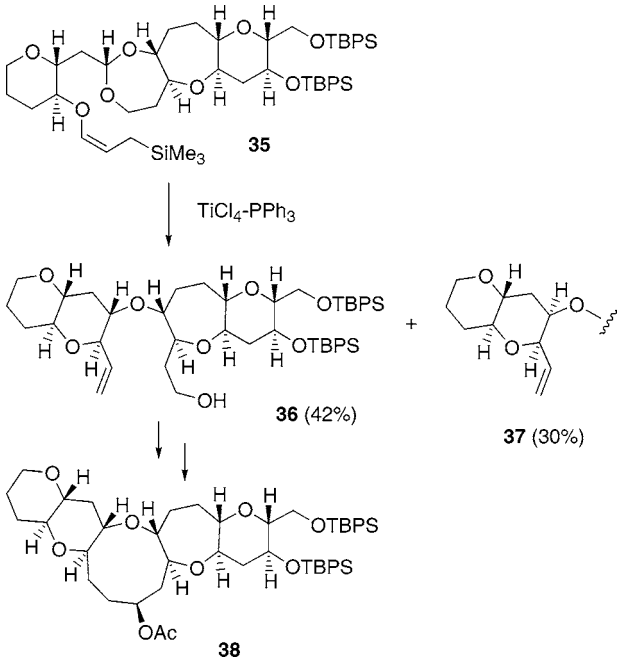


substrate	ratio (**29** : **30**)	yield (%)
28	93 : 7	51
31	37 : 63	38

Scheme 9



Scheme 10



Convergent Synthesis via the Intramolecular Allylation of α-Acetoxy Ethers

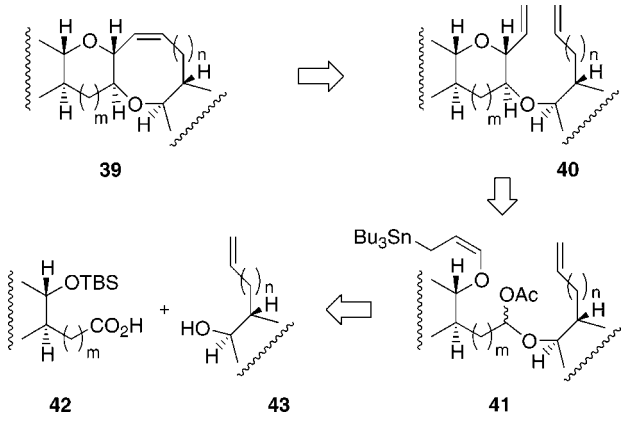
Because most of the marine polycyclic ethers have a large number of fused cyclic ether frameworks, an efficient synthesis of these giant molecules requires a convergent strategy, instead of the linear one mentioned above. The intramolecular allylation of acetal derivatives and its equivalents was considered as a promising method for assembling polycyclic ether segments.

At the beginning of our study for the synthesis of cyclic ethers, we examined the cyclization of γ-alkoxy allylmetals with chiral acetals as shown in Scheme 8.[22] Treatment of allylic stannane **28** with $TiCl_4$−PPh_3 afforded **29** in reasonable yield with high diastereoselectivity. On the other hand, the reaction of the allylsilane derivative **31** gave the diastereoisomer **30** as the major product, although the selectivity and yield were moderate. The reversal of stereoselectivity can be explained by the difference in the timing of the bond breaking and making between the silicon and the tin reagents.[23] The cyclization of the reactive allylic stannane **28** would proceed via a S_N2 like transition state, whereas the less reactive silicon derivative **31** would react in a S_N1 manner.

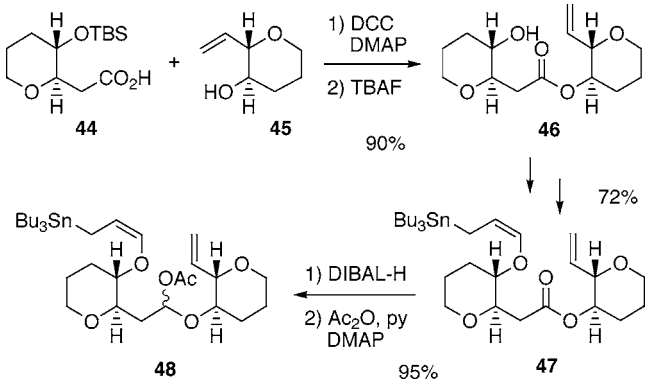
Martín and co-workers applied this reaction to the convergent assembly of ether rings. The reaction of the allylic stannane **32** having a tetrahydropyran ring on the acetal moiety with $TiCl_3(O^iPr)$ gave **33** as the predominant product in 73% yield (Scheme 9).[24] The product **33** was converted to the tricyclic ether **34** via the thioether formation and desulfo-olefination. Unfortunately, the stereochemistry of the product **34** through this ring fusion does not correspond to that of natural polycyclic ethers. Sasaki and Tachibana reinvestigated the reaction of **32** and confirmed that the allylation via allylic stannane gave undesired stereoselectivity.[25]

On the other hand, Sasaki and Tachibana designed the substrate **35** having an allylic silane moiety as a weak

Scheme 11

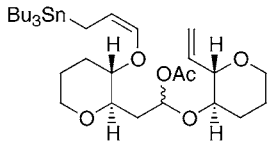
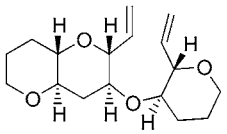
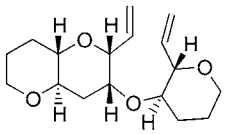
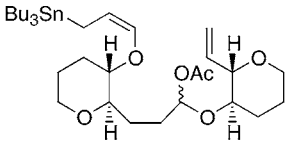
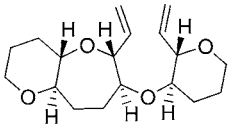
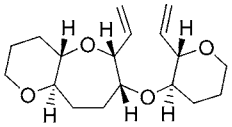
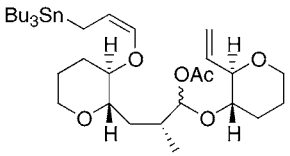
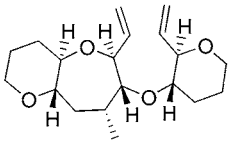
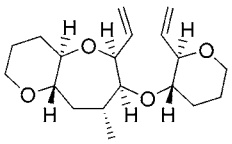
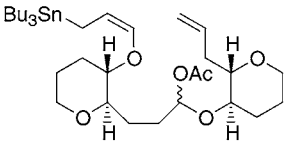
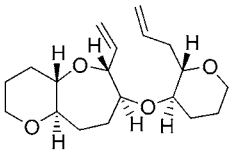
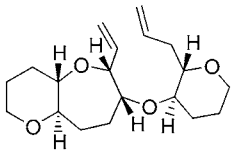
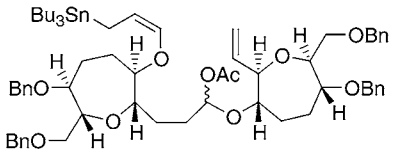
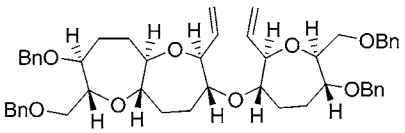
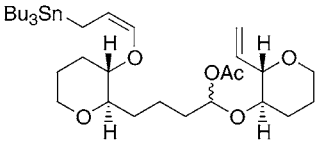
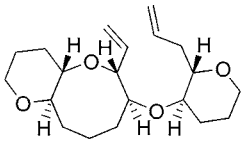
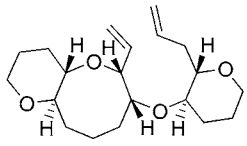
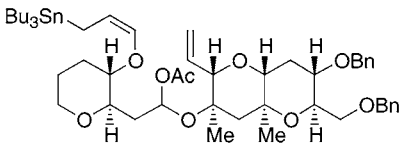
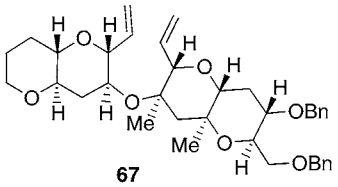
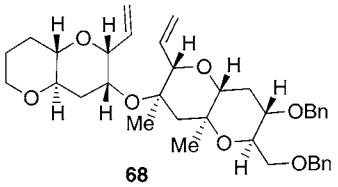
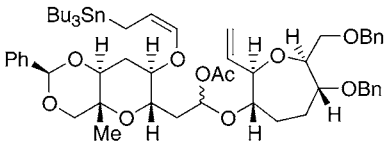
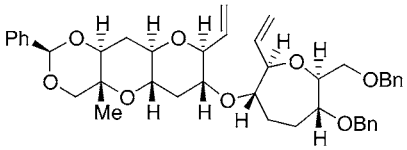


Scheme 12[a]



[a] DCC = 1,3-dicyclohexylcarbodiimide; DMAP = 4-(dimethylamino)pyridine; TBAF = tetrabutylammonium fluoride; DIBAL-H = diisobutylaluminum hydride.

Table 1. Intramolecular Reaction of γ-Alkoxyallylstannane and α-Acetoxy Ether[a]

entry	substrate	products			yield
1[b]	 **48**	 **56**	+ 70:30	 **57**	79%
2	 **49**	 **58**	+ >95:5	 **59**	73%
3	 **50**	 **60**	+ 82:18	 **61**	93%
4	 **51**	 **62**	+ 87:13	 **63**	67%
5	 **52**	 **64**			64%
6	 **53**	 **65**	+ >95:5	 **66**	60%
7	 **54**	 **67**	+ 71:29	 **68**	95%
8	 **55**	 **69**			74%

[a] Reactions were carried out with 4 equiv of $MgBr_2 \cdot OEt_2$ in CH_2Cl_2. [b] $BF_3 \cdot OEt_2$ was used as a Lewis acid.

nucleophile (Scheme 10).[26] Treatment of **35** with $TiCl_4$–PPh_3 gave the desired compound **36** and the stereoisomer **37** in 42% and 30% yields, respectively. The compound **36** was converted to the pentacycle **38**, a part of ciguatoxin (**3**), via a SmI_2-mediated intramolecular Reformatsky reaction. Although the desired isomer **36** was obtained as

the major product, the yield and stereoselectivity remained moderate.

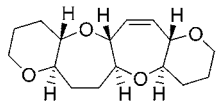
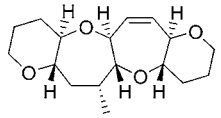
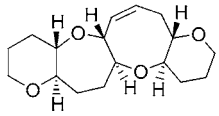
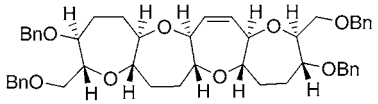
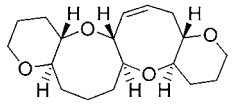
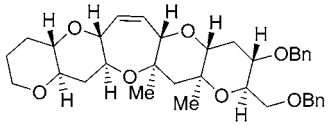
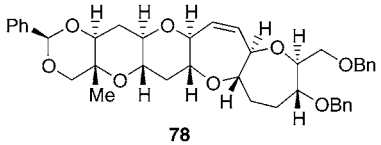
These problems prompted us to develop a new method for the convergent synthesis of polycyclic ethers. A new synthetic methodology is decribed in Scheme 11.[27] Over the past few years, transition metal catalyzed ring-closing metathesis has been well recognized as a powerful tool for the synthesis of cyclic ethers.[28,29] The retro ring-closing metathesis of **39** leads to the diene **40**. The crucial point of our strategy is the convergent synthesis of the key intermediate **40**. We planned to use α-acetoxy ethers as electrophiles for the intramolecular allylations.[30] Retrosynthetic disassembly of the cyclization precursor **41** affords the carboxylic acid **42** and the alcohol **43**.

The preparation of a cyclization precursor is shown in Scheme 12. The 1,3-dicyclohexylcarbodiimide (DCC) coupling of the carboxylic acid **44** and the alcohol **45** followed by desilylation afforded the ester **46** in 90% yield. The alcohol was converted to the allylic stannane **47** via the acetal formation and cleavage method described in Scheme 6. Partial reduction of **47** with diisobutylaluminum hydride (DIBAL-H), followed by treatment of the resulting aluminum hemiacetal with Ac_2O/pyridine/4-(dimethylamino)-pyridine (DMAP) gave **48** as a mixture of diastereoisomers in 95% yield.[30,31]

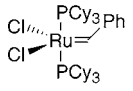
The cyclization precursors **49**−**55** were prepared in a similar manner, and the results of the cyclization are summarized in Table 1. Treatment of **48** with 4 equiv of BF_3·OEt_2 gave a 70:30 mixture of the cyclized products **56** and **57** in 79% yield (entry 1). Higher stereoselectivities were observed in the formation of seven-membered rings; the reactions of **49**−**52** with $MgBr_2$·OEt_2 afforded the corresponding cyclic ethers **58**, **60**, **62**, and **64**, respectively, as major products (entries 2−5). It should be noted that the desired stereoisomer **60** was obtained predominantly from the reaction of **50**, which has a methyl substituent at the α-position of acetoxy group. This result is very promising and would allow us to synthesize the CDEF ring system of brevetoxin B (**1**) in a stereoselective and convergent manner. The generality of this reaction is demonstrated by eight-membered ring formation. Thus, the reaction of **53** gave **65** in 60% yield with very high stereoselectivity (entry 6). In our initial study for the total synthesis of gambierol (**4**), one of the most difficult problems that we had encountered was the introduction of two bridgehead methyl groups of the EFG ring. We examined several conceivable approaches to this problem, but all the attempts resulted in failure.[32] However, the model substrate **54** could be synthesized rather easily from the corresponding tertiary alcohol, and the cyclization with $MgBr_2$·OEt_2 gave a 71:29 mixture of **67** and **68** in 95% yield (entry 7). The relatively mild reaction conditions employed allowed the use of **55**, having an acetal protective group, as a substrate to give **69** in 74% yield with very high stereoselectivity (entry 8).

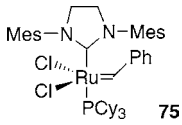
We next examined the ring-closing metathesis of the products (Table 2). Treatment of **58** with the Grubbs catalyst **70**[33] gave the tetracyclic ether **71** in 91% yield (entry 1). The reaction of **60** provided **72**, corresponding

Table 2. Ring-Closing Metathesis of Dienes[a]

entry	substrate	product	yield
1	**58**	 **71**	91%
2	**60**	 **72**	86%
3	**62**	 **73**	64%
4	**64**	 **74**	84%
5[b]	**65**	 **76**	87%
6[b]	**67**	 **77**	84%
7[b]	**69**	 **78**	50%

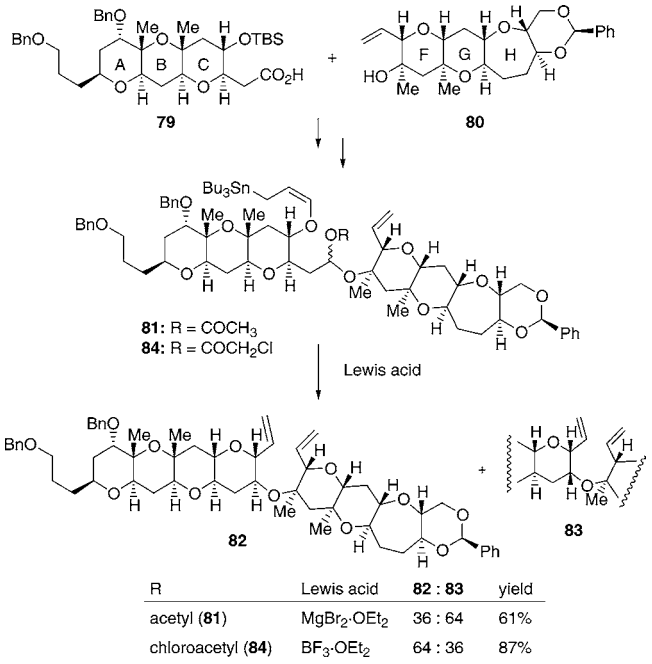
[a] Reactions were carried out with 20 mol % of **70**. [b] Reactions were carried out with 20−40 mol % of **75**.


70


75

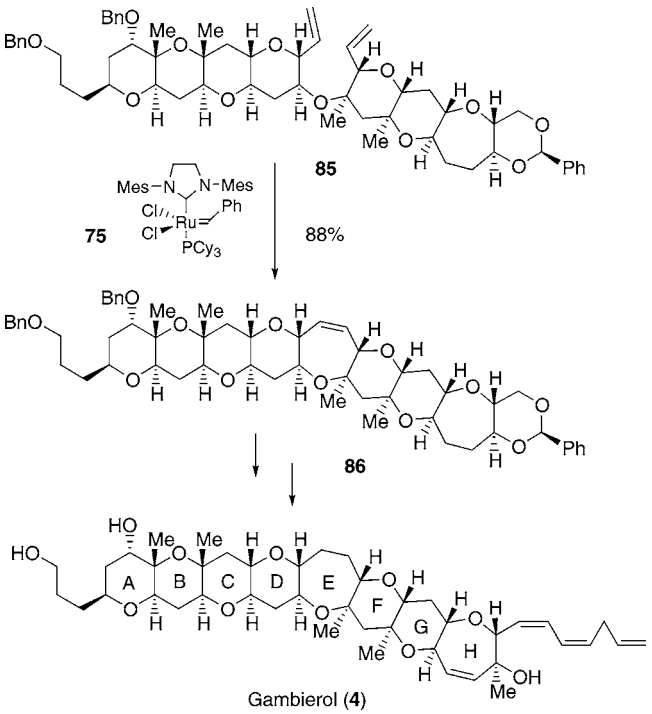
to the CDEF ring system of brevetoxin B (**1**), in 86% yield (entry 2). Similarly, the reactions of **62** and **64** proceeded smoothly to afford the tetracyclic ethers **73** and **74** in 64% and 84% yields, respectively (entries 3 and 4). Although the reaction of **65** with **70** gave **76** in 49% yield along with 28% of the starting material, the use of the more active catalyst **75**[34] provided the 6,8,8,6-tetracyclic system **76** in 87% yield (entry 5). Similarly, treatment of **67** with **75** provided the pentacyclic ether **77**, corresponding to the CDEFG ring system of gambierol (**4**), in 84% yield (entry 6). Although the reason is not clear, the reaction of **69** was very slow and afforded **78** in moderate yield (50%, entry 7).

Scheme 13



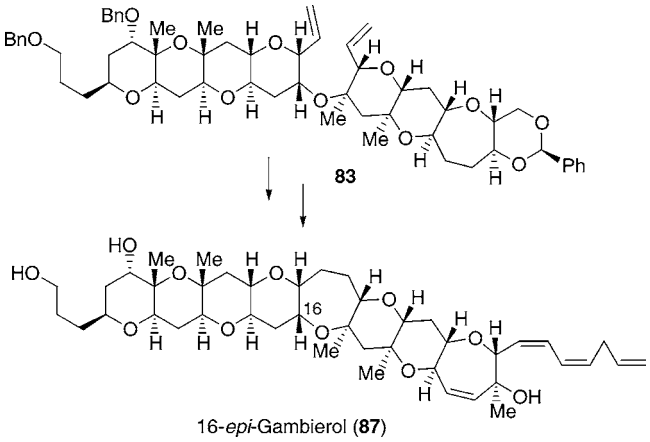
R	Lewis acid	**82** : **83**	yield
acetyl (**81**)	$MgBr_2 \cdot OEt_2$	36 : 64	61%
chloroacetyl (**84**)	$BF_3 \cdot OEt_2$	64 : 36	87%

Scheme 14

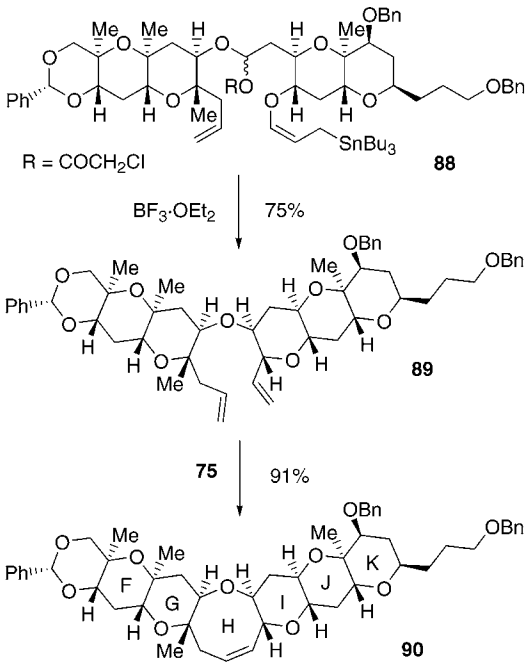


Encouraged by the performance of this methodology, we focused on the total synthesis of gambierol (**4**).[12c,d] The ABC and FGH ring segments **79** and **80** were converted to the α-acetoxy ether **81** by the same procedure described before (Scheme 13). Treatment of **81** with $MgBr_2 \cdot OEt_2$ afforded a mixture of the desired product **82** and its epimer **83** in 61% yield. Unfortunately, the undesired stereoisomer **83** was obtained as the major component. After several unfruitful attempts, we found conditions giving the desired product predominantly. Treatment of the α-chloroacetoxy ether **84** furnished **82** and **83** in the ratio of 64:36 in 87% yield. We assume that the greater

Scheme 15



Scheme 16

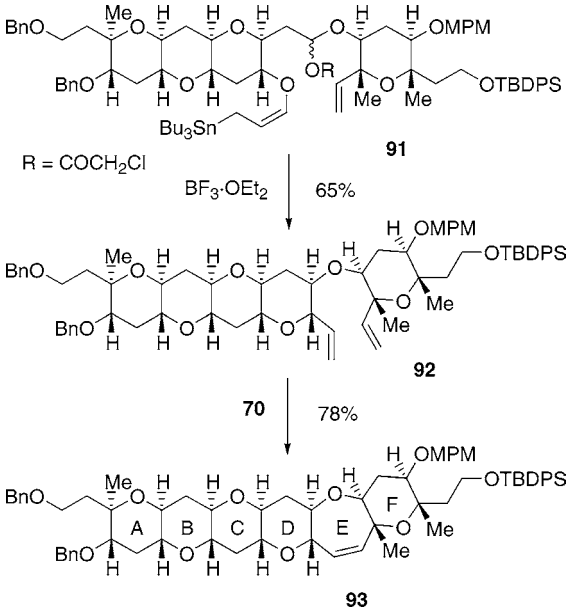


ability of the chloroacetoxy moiety to act as a leaving group when compared to the acetoxy group drives the reaction to proceed through an S_N1 pathway giving the desired isomer **82** predominantly.

The diene **85** obtained was then subjected to the ring-closing metathesis using the second generation Grubbs catalyst **75** leading to the octacycle **86** in 88% yield (Scheme 14). Modification of the H ring and side chain elongation completed the total synthesis of gambierol (**4**). The longest linear sequence from the commercially available starting material, 2-deoxy-D-ribose, to **4** is 66 steps with 1.2% overall yield, and the total number of the steps is 102.

Similar transformations starting from the isomer **83** afforded the 16-epi-gambierol (**87**), which was subjected to a biological assay using mice (Scheme 15).[12d] Interestingly, the epimer **87** exhibited no toxicity at a concentration of 14 mg/kg, which is 300 times as much as the LD_{50} value (50 μg/kg) reported for the natural product. This result indicates that the trans-fused poly-

Scheme 17[a]



[a] MPM = 4-methoxyphenylmethyl; TBDPS = *tert*-butyldiphenylsilyl.

cyclic ether framework is essential to the toxicity. To the best of our knowledge, this is the first example of a biological investigation on a "cis-fused" polycyclic ether compound.

Two more examples for our synthetic studies on polycyclic ethers are illustrated in Schemes 16 and 17. The reaction of **88** with $BF_3{\cdot}OEt_2$ provided the diene **89** as a single stereoisomer in 75% yield. The ring-closing metathesis of **89** gave **90**, corresponding to the F−K ring segment of brevetoxin B (**1**), in 91% yield.[35] Similarly, the intramolecular allylation of **91** followed by ring-closing metathesis of **92** afforded the hexacycle **93**, the A−F ring system of yessotoxin (**5**).[36]

Conclusion

We have developed two important methods for the stereoselective synthesis of polycyclic ethers via intramolecular allylations, the allylstannane−aldehyde condensation for the iterative synthesis and the reaction of α-acetoxy ethers followed by ring-closing metathesis for the convergent assembly. These reactions proceed with a high level of stereocontrol and with high tolerance of labile functional groups. The usefulness of these methodologies has been demonstrated by the total syntheses of hemibrevetoxin B (**2**) and gambierol (**4**). Synthetic studies of other polycyclic ethers including brevetoxin B (**1**) and yessotoxin (**5**) are in progress in our laboratory.

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